Applicants acknowledge, with appreciation, withdrawal of the objection related to the priority claim.

The Office Action states that the claims embrace genomic clones of TRELL as well as polynucleotides comprising introns, flanking sequences, etc. Applicants hereby amend the claims to embrace polynucleotides encoding TRELL which do not contain introns. The specification also clearly defines what is meant by "substantially pure nucleic acid" at page 10, lines 8-20. Thus, the claims, as amended do not embrace genomic clones containing introns. However, the claims have not been amended to exclude flanking sequences. Such a limitation is unduly restrictive and is contrary to the practice of the United States Patent Office. An applicant for patent is entitled to claim his invention as broadly as possible, commensurate with the scope of the disclosure and circumscribed by the teachings of the prior art. Claims to nucleic acid sequences are typically worded with the open term "comprising" to include additional nucleotides which may be appurtenant to the main feature described (typically a SEQ ID NO).

In the present case, the applicants clearly describe and enable, for example, nucleic acid sequences encoding TRELL having specific amino acid sequences operatively linked to expression control sequences (see, for example, page 7, lines 19-22; page 11, lines 31-34 through page 12, lines 1-29). Moreover, one of ordinary skill in the art is well-equipped with the knowledge necessary to easily operatively link various expression control sequences to the TRELL encoding sequence. Thus, the Examiner's insistence on limiting the nucleic acid claims to the precise nucleotides disclosed is unduly restrictive in light of the disclosure, the knowledge within the purview of the skilled artisan, and with generally accepted practice in the U.S. Patent Office. Applicants respectfully request withdrawal of the rejection of the claims on this ground.

Applicants have amended claim 4 to recite identity to the C-terminal, extracellular binding domain of TRELL. The Specification refers to the C-terminal receptor binding domain at page 7, lines 15-18, and this portion is again referred to, with respect to the human sequence at page 14, lines 26-29 as the 204 amino acid extracellular domain. This portion is obviously the C-terminal region, as the N-terminus and the 27 amino acid transmembrane portion are described previously in this passage. The applicants have further amended claim 4 to clarify that the encoded protein identified through hybridization contains a portion that is 50% identical to the extracellular domain of *human* TRELL, and have specifically identified the amino acids for which one of skill in the art assesses 50% identity.

Moreover, the Applicants have clearly described assays that show the binding of TRELL to a variety of cells. One of ordinary skill in the art is thus given sufficient guidance with respect to determining whether the nucleic acid sequences that encode a protein that comprises a portion that is at least 50% identical to the extracellular domain of SEQ ID NO:2 or SEQ ID NO:4 also contains the biologically active component of the TRELL molecule.

Thus, the amendment to the claim is fully supported by the disclosure and contains sufficient chemical/structural information regarding the genus claimed and functional assays to assess function of the encoded proteins. Applicants were in possession of the claimed genus, as instantly claimed. The inventors could envision the detailed constitution of the molecules so as to distinguish them from other materials. See *Amgen v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q.2d 1016, 1021 (Fed Cir. 1991).

**35 U.S.C. § 112, First Paragraph: Enablement**

The Office Action rejects claims 4, 5 and 28-31 under 35 U.S.C. § 112, First Paragraph as allegedly non-enabled. The Examiner states that only molecules encoding the exact same

amino acids as SEQ ID NO:2 or SEQ ID NO:4 are enabled, and only in *in vitro* applications. Applicants strongly disagree both with the legal and scientific aspects of the rejection.

The Office Action notes that claims 4 and 5 embrace nucleic acid sequences that encode polypeptides containing deletions, alterations and substitutions that do not abolish TRELL binding activity. The Examiner also notes that the Specification specifically discloses a functional test for TRELL binding activity. Furthermore, the Applicants specifically disclose that the extracellular domain of TRELL contains the portion of the protein that mediates the binding activity.

Claims 4 and 5 have been amended to include the feature that the polypeptide sequences are at least 70% identical to the extracellular domain of TRELL and that the amino acid alterations, deletions or substitutions do not abolish the ability of the polypeptides to bind to cells that are bound by SEQ ID NO:2 or SEQ ID NO:4. One of ordinary skill in the art could easily determine which polypeptides include these features. No more than routine experimentation would be required as the Applicants have provided ample guidance with respect to the manner in which experimentation may be performed, by a variety of cell types that may be used in the assays and through a description of the extracellular domain, representative amino acid sequences and the disclosure that the extracellular domain of TRELL contains the region responsible for such biological activity. The law is clear that ***even a large amount of experimentation is permissible*** as long as the amount of experimentation is not undue (see MPEP 2164.06, Rev. 1 Feb. 2000, citing *In re Wands* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)(emphasis added). The Examiner's reliance on Rudinger and Ngo *et al.* is misplaced. The passage quoted from Rudinger appears to refer to ones ability to predict which amino acid sequences in a given protein are significant for biological activity by examination of the

sequence itself. Rudinger refers to experimental study as the key to understanding biological activity. Notably, the Applicants have studied TRELL and have determined a variety of significant biological features that are disclosed and described in the present application. The Applicants have determined the amino acid sequences of two related TRELL polypeptides (from mouse and human sources). The Applicants have further determined that the TRELL proteins are single transmembrane-spanning proteins that have a 27 amino acid transmembrane portion. Applicants have also determined that the N-terminus is the cytoplasmic portion of the protein and that the C-terminus is involved with receptor binding. These teachings make it a matter of routine experimentation to express variants of TRELL within the scope of the claims and to determine whether biological activity is abolished. This amount of experimentation is a far cry from what the Examiner is insinuating to be the kind of experimentation required and the relationship of this experimentation to the law as set forth in *In re Fisher*.

Likewise, Ngo *et al.* refers to predicting biological features from the bare amino acid sequences. This is not what the Applicants have done, nor is that what is required by the claims to determine what molecules fall within their scope. Applicants have provided more than mere amino acid sequence. As described above, Applicants have described structural and functional information regarding TRELL to guide the skilled artisan.

The Examiner appears to state that one of skill in the art could not even make a single conservative substitution in the disclosed TRELL proteins and assay it using the disclosed assays to determine whether binding activity was abolished. Clearly, this is incorrect. One of skill in the art could make numerous substitutions and deletion mutants and test them using the disclosed assays by routine experimentation. Such is clearly permissible by the existing case law.

Applicants urge the Examiner to withdraw this rejection.

Applicants have added claims 36-38, drawn to methods of expressing TRELL in mammalian cells *in vitro*. The Examiner has indicated that objections to such method claims could be overcome by adding the limitation "*in vitro.*" Therefore, it is believed that claims 36-38 are allowable as presented.

Claims 28-31, however, have not been amended to include the limitation "*in vitro.*" The claims as presented are drawn to methods of expressing TRELL in mammalian cells, not to gene therapy, *per se.* The Applicants have provided teaching as to the utility of expressing TRELL in cells, and the utility of expressing gene products in cells is readily apparent to those of skill in the art. Expression systems for expressing proteins in mammalian cells were well-known in the art at the time of filing. Not only is one of ordinary skill in the art provided with general guidance as to the selection of expression system, but the skilled artisan is also provided with guidance as to the modification which may be introduced and the factors which may influence this decision. It is well-settled that an Applicant for patent need not disclose in the Specification what is known in the art, and preferably omits what is already known and available to the public (*In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); See also MPEP 2100-180, August 2001).

With respect to gene therapy, the Applicants state that the Tumor Necrosis Factor Related Ligand (TRELL) may be used to "enhance anti-tumor responses or directly affect the survival of the tumor." Thus, the expression of TRELL *participates* in anti-tumor responses. Thus, expression of TRELL in these cells is expected to have a positive effect on the existing anti-tumor response. The application of this technology is generally applicable to tumors. All that is required is expression of TRELL in mammalian cells as instantly claimed. Moreover, it

is not a requirement that the Applicants provide working examples for every type of tumor known. In fact, working examples are not a requirement at all.

Likewise, the Applicants teach that the Tumor Necrosis Factor Related Ligand (TRELL) may affect the survival of an organ graft by altering the local immune response. In this regard, the Applicants teach at page 13, lines 21-22, that TRELL may be introduced into the graft itself, or to the surrounding cells. TRELL expression in these cells is expected to positively affect the survival of an organ graft by inhibiting the local immune response. Again, all that is required is expression of TRELL in mammalian cells as instantly claimed.

Applicants urge the Examiner to reconsider the rejection of these claims on this ground.

**New Objections**

Turning to the new rejections cited in the Office Action, the Applicants have amended the claims to recite the precise words defined in the Specification at page 10, lines 8-20. In this definition, it is clear that the sequences encoding TRELL, when substantially pure, do not include additional sequence with which it occurs in the organism from which it is derived. Thus, the Applicants have particularly pointed out and distinctly claimed this subject matter. The Examiner's point that "substantially" is a relative term is misplaced, as this term is specifically defined in the Specification at page 8, lines 8-14. Moreover, it is well-settled that claim language may include relative terms, and such terms do not automatically render a claim indefinite (*Seattle Box Co. v. Industrial Crating & Packaging, Inc.* 221 U.S.P.Q. 568 (Fed. Cir. 1984)). What is required is that one of skill in the art would understand what is claimed in light of the Specification. In the instant case, the Applicants have clearly defined the term.

Claim 4 has been amended to recite the precise amino acids of human TRELL rather than "receptor binding domain of TRELL." Thus, this basis of rejection is moot.

Claim 5 has been amended to clarify that the DNA encodes an analog of TRELL in which the amino acid sequence is a disclosed TRELL sequence having conservative amino acid substitutions or deletions that do not affect the binding ability of the molecule. Support for this amendment may be found, for example, at page 18, lines 23-26.

Claim 5 has been further amended to clarify a biological activity of TRELL which may be assessed, namely binding of the analog to cells that normally bind native TRELL. Support for the amendment may be found, for example, at pages 36-37.

We earnestly submit that the claims are condition for allowance, which action is respectfully requested.

Respectfully submitted,

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Date: May 28, 2002

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**Version with Markings to Show Changes Made**

**IN THE CLAIMS**

1. (Three Times Amended) [An isolated] A substantially purified nucleic acid [molecule] comprising consecutive nucleotides that [encoding] encode TRELL, wherein said TRELL comprises the amino acid sequence SEQ ID NO:2 or SEQ ID NO:4.

2. (Three Times Amended) A substantially [purified DNA molecule encoding] pure nucleic acid comprising consecutive nucleotides that encode TRELL, said [sequence] nucleic acid consisting essentially of SEQ ID NO:1 or SEQ ID NO:3.

3. (Three Times Amended) A substantially [purified DNA molecule] pure nucleic acid consisting essentially of SEQ ID NO:1 or SEQ ID NO:3, said [DNA] nucleic acid encoding a polypeptide, said polypeptide consisting essentially of SEQ ID NO:2 or SEQ ID NO:4.

4. (Three Times Amended) A substantially [purified DNA molecule] pure nucleic acid that hybridizes under stringent conditions to at least a fragment of SEQ ID NO:1 or SEQ ID NO:3, said fragment comprising at least 20 consecutive bases, said [DNA sequence] nucleic acid encoding a polypeptide comprising a portion that is at least 50% [homologous] identical with [the receptor binding extracellular domain of TRELL] amino acids 81-284 of SEQ ID NO:4, wherein said stringent conditions comprise washing steps using 2X SSC, 0.1% SDS at 65°C.

5. (Three Times Amended) A substantially [purified DNA molecule] pure nucleic acid wherein said nucleic acid comprises consecutive nucleotides encoding an analog of [molecule encodes] TRELL, wherein said analog of TRELL comprises the amino acid sequence SEQ ID NO:2 or SEQ ID NO:4, except wherein said amino acid sequence comprises conservative substitutions[, alterations] or deletions which do not [abolish]

prevent the [biological activity of] the binding of said analog of TRELL to cells that bind to the polypeptides of SEQ ID NO:2 or SEQ ID NO:4.

6. (Twice Amended) The nucleic acid [molecule] of claim 1 operably linked to an expression control sequence.

7. (Three Times Amended) The nucleic acid [molecule] of claim 6 comprising SEQ ID NO:1 or SEQ ID NO:3.

8. (Twice Amended) A host cell transformed with the nucleic acid [molecule] of claim 6 or 7.

28. (Twice Amended) A method of expressing TRELL in a mammalian cell comprising:

a. introducing a vector comprising a nucleic acid molecule comprising [a sequence] consecutive nucleotides encoding TRELL into a mammalian cell, wherein said TRELL comprises the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4;

b. allowing said cell to live under conditions wherein said nucleic acid molecule is expressed in said mammalian cell.

36. (New) A method of expressing TRELL in a mammalian cell *in vitro* comprising:

a. introducing a vector comprising a nucleic acid molecule comprising consecutive nucleotides encoding TRELL into a mammalian cell, wherein said TRELL comprises the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4;

b. allowing said cell to live under conditions wherein said nucleic acid molecule is expressed in said mammalian cell.

37. (New) The method of claim 36 wherein said mammalian cell is a human cell.

38. (New) The method of claim 36 wherein said vector is a virus.